15/Declaration

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: David S. WELLS, et al.

Title: SUSTAINED-RELEASE FORMULATIONS FOR TREATING CNS-MEDIATED DISORDERS

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Examiner: L. Channavajjala

Art Unit: 1615

DECLARATION OF MANUEL F. BALANDRIN

I, Manuel F. Balandrin, R.Ph., Ph.D., declare that:

1. I am a Registered Pharmacist and the Senior Research Scientist, Medicinal Chemistry at NPS Pharmaceuticals, Inc., where I have been employed since 1988. Education: College of Pharmacy, University of Madrid, Spain (1970-73) and College of Pharmacy & Graduate College, Medical Center, University of Illinois at Chicago (1974-82), B.S. in Pharmacy with Honors (*cum laude*, 1977) and Ph.D. [Pharmacognosy (Medicinal Chemistry of Natural Products), 1982]. Over 50 publications and 20 U.S. and International patents, patents pending, and patents applications. Co-inventor of three compounds currently in human clinical trials in the U.S., U.K., and Japan. One of these, cinacalcet hydrochloride [also known as AMG 073 and NPS 1493 (U.S. Pat. 6,211,244)], is currently being evaluated by co-developers Amgen (in the U.S.) and Kirin Pharmaceuticals (in Japan) in late-stage (Phase II/III) human clinical trials for the treatment of hyperparathyroidism (HPT) and parathyroid cancer. Other co-invented clinical candidate drug products which have successfully completed (Phase I) human safety studies in clinical trials include NPS 1776 [isovaleramide (U.S. Pats. 5,506,268, 5,763,494, and 6,383,527), for the treatment of acute migraine, bipolar disorder, spasticity, and epilepsy], and NPS 1506 [(U.S. Pat. 6,017,965) for the treatment of acute depression and stroke]. Honors and Awards include:

S.B. Penick Memorial Fellow (American Foundation for Pharmaceutical Education), Rho Chi (National Pharmaceutical Honor Society), Phi Kappa Phi Honor Society; Platinum Award, Division of Agricultural and Food Chemistry, American Chemical Society, 1996; listed in *American Men and Women of Science* and *1000 World Leaders of Scientific Influence* (American Biographical Institute, 2002); recently nominated to *Who's Who in Science and Engineering*.

2. I determined the values for the calculated logarithm of the (octanol:water) partition coefficient (clogP, a "hydrophobicity descriptor") and predicted solubilities of isovaleramide and *N,N*-diethylisovaleramide, using software by Advanced Chemistry Development, Inc. Isovaleramide has clogP value of 0.18 (± 0.23); *N,N*-diethylisovaleramide has a clogP value of 1.73 (± 0.25). The clogP results indicate that isovaleramide is much more hydrophilic ("water-loving") and much less lipophilic ("fat-loving") than *N,N*-diethylisovaleramide; conversely, *N,N*-diethylisovaleramide is much more hydrophobic ("water-fearing") and much more lipophilic than isovaleramide. Isovaleramide has a predicted solubility in water of 60 g/L, whereas *N,N*-diethylisovaleramide's solubility is predicted to be 5 g/L. Isovaleramide is therefore predicted to be about twelve times more soluble in water than *N,N*-diethylisovaleramide. These results are consistent with THE MERCK INDEX (12th ed. 1996), which states that isovaleramide crystals are "Sol[uble] in water" (monograph no. 5250, p. 893), and that, for *N,N*-diethylisovaleramide, "One gram [of the oily liquid] dissolves in about 25 ml of water..." (monograph no. 5253, page 893). In other words, the water-solubility of *N,N*-diethylisovaleramide is only about 4% w/v(weight/volume).

3. Drug excretion tends to be fast, and localization (accumulation) of drug in fatty tissue low, for water-soluble, hydrophilic compounds such as isovaleramide. *See* Tute & Kier, PRINCIPLES OF MEDICINAL CHEMISTRY (4th ed. 1995), at p. 50-57. Thus, the pharmaceutical half-lives of water-soluble, hydrophilic compounds such as isovaleramide are generally shorter than those of water-insoluble, hydrophobic compounds such as *N,N*-diethylisovaleramide. It is well known that controlled-release formulations are most appropriate for drugs with short half-lives. *See* GOODMAN & GILMAN'S THE PHARMACOLOGIC BASIS OF THERAPEUTICS (10th ed. 2001), at p. 6.

4. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and

the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

April 10, 2003
Date

Manuel F. Balandrin
Manuel F. Balandrin